# Complete Summary

## GUIDELINE TITLE

American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer.

## BIBLIOGRAPHIC SOURCE(S)

Loblaw DA, Mendelson DS, Talcott JA, Virgo KS, Somerfield MR, Ben-Josef E, Middleton R, Porterfield H, Sharp SA, Smith TJ, Taplin ME, Vogelzang NJ, Wade JL Jr, Bennett CL, Scher HI. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. J Clin Oncol 2004 Jul 15;22(14):2927-41. [59 references] PubMed

## COMPLETE SUMMARY CONTENT



## SCOPE

### DISEASE/CONDITION(S)

Metastatic or recurrent androgen-sensitive prostate cancer

### GUIDELINE CATEGORY

Management
Treatment

### CLINICAL SPECIALTY

Oncology
Radiation Oncology
Urology

## INTENDED USERS

Physicians

## GUIDELINE OBJECTIVE(S)

To provide recommendations on the use, combinations, and timing of various forms of androgen deprivation therapy (ADT) for the palliation of men with androgen-sensitive disease

## TARGET POPULATION

Men with metastatic or recurrent androgen-sensitive prostate cancer

## INTERVENTIONS AND PRACTICES CONSIDERED

### Standard Initial Treatment Options

1. Bilateral orchiectomy
2. Medical castration with luteinizing hormone releasing hormone (LHRH) agonists
3. Diethylstilbestrol (DES) is no longer commercially available in North America and is not recommended as a standard first-line treatment option
4. Patient education/counseling

### Castration Alternatives

1. Nonsteroidal antiandrogen monotherapy (e.g., flutamide, nilutamide, and bicalutamide)
2. Steroidal antiandrogen(e.g., cyproterone acetate) is not recommended as monotherapy

### Combination Therapy

Medical or surgical castration plus a nonsteroidal antiandrogen

## MAJOR OUTCOMES CONSIDERED

- Overall survival
- Progression-free survival
- Toxicity of treatment
- Time to treatment failure
- Disease progression
- Complications due to progression
- Cost-effectiveness
- Time off therapy
- Time to hormone resistance
- Quality of life

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

#### Methods Overview

An expert panel and writing committee were formed. The questions to be addressed by the guideline were determined, and a systematic review of the literature was performed, which included a search of online databases, bibliographic review, and consultation with content experts.

#### Literature Review and Data Collection

The Medline database (1966 through March 2003; National Library of Medicine, Bethesda, MD) was searched to identify relevant information from the published literature. A series of searches was conducted using the medical subject headings "prostatic neoplasms" and "androgen antagonists," and the text words intermittent," "combined androgen," and "metastatic." These terms were combined with the following study design-related subject headings or text words: "meta-analysis," "systematic," trial," and "randomized." Search results were limited to human studies and English-language articles.

In addition, the Cochrane Database of Systematic Reviews was searched using the phrase "prostate cancer," and directed searches were made of the reference lists from primary articles. Authors were contacted for clarification where needed. The Physician Data Query clinical trials database (http://www.cancer.gov/search/clinical_trials/) was searched for ongoing clinical trials in the identified subject areas.

#### Inclusion Criteria

Table 1 in the original guideline document describes the details of the inclusion criteria and outcome variables for each question addressed.

#### Exclusion Criteria

For each question, the following types of evidence were not considered: (1) letters and editorials, (2) papers published in a language other than English.

In addition, for questions 4 (early versus deferred androgen deprivation therapy [ADT]) and 5 (intermittent versus continuous androgen deprivation therapy), the following were excluded: (1) participants previously treated with hormonal therapy, (2) randomized clinical trials targeting men undergoing radiation as primary therapy, (3) nonrandomized prospective studies, (4) retrospective

studies, and (5) randomized clinical trials targeting men with clinically localized but not pathologically advanced prostate cancer.

## NUMBER OF SOURCE DOCUMENTS

There were 10 randomized controlled trials, six systematic reviews, and one Markov model available to inform the guidelines.

## METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

## METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The original Panel met four times. The first meeting was intended to identify topics to be addressed by the guideline, to develop a strategy for completion of the guideline, and to do a preliminary review of the initial literature search; at the second meeting, the Panel reviewed the developed guideline and evaluated more critically the recommendations and supporting evidence. The guideline was circulated in draft form.

The draft guideline was submitted to the American Society of Clinical Oncology (ASCO) Health Services Committee (HSC) for review and approval in October 2002. Based on its review, the HSC recommended revisions to the draft.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

## COST ANALYSIS

The Panel considered the comparative costs of clinical strategies in formulating recommendations for the use of androgen deprivation therapy (ADT). While the published clinical trials identified did not include formal cost-effectiveness analyses, some articles used data from these trials to develop cost-effectiveness estimates.

### METHOD OF GUIDELINE VALIDATION

Internal Peer Review

### DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The content of the guidelines and the manuscript were reviewed and approved by the Health Services Committee (HSC) and by the American Society of Clinical Oncology (ASCO) Board of Directors before dissemination.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

For men with metastatic or recurrent androgen-sensitive prostate cancer, in whom androgen deprivation therapy (ADT) is considered the most appropriate initial intervention:

1. What are the standard initial treatment options?

   Recommendation: Bilateral orchiectomy or medical castration with luteinizing hormone releasing hormone (LHRH) agonists are the recommended initial treatments for metastatic prostate cancer. A full discussion between practitioner and patient should occur to determine which is best for the patient. Diethylstilbestrol (DES) should not be considered as a standard first-line treatment option and is currently no longer commercially available in North America.

2. Are antiandrogens as effective as other castration therapies?

   Recommendation: Nonsteroidal antiandrogen monotherapy may be discussed as an alternative to castration. Steroidal antiandrogens should not be offered as monotherapy.

3. Is combined androgen blockade better than castration alone?

   Recommendation: A discussion should occur between the patient and his practitioner. The patient needs to appreciate that there is a small potential gain in overall survival (OS) with the addition of a nonsteroidal antiandrogen to medical or surgical castration and that increased side effects may occur as a result.

4. Does early ADT improve outcomes over deferred therapy?

Recommendation: Until data from studies using modern medical diagnostic and biochemical tests and standardized follow-up schedules become available, no specific recommendations can be issued by the Panel regarding the question of early versus deferred ADT using LHRH agonists or orchiectomy. A discussion about the pros and cons of early versus deferred therapy should occur between patient and practitioner. Antiandrogen monotherapy is not recommended. Patients should be followed clinically and started on ADT once symptoms of locally progressive or metastatic disease present.

5. Is intermittent ADT better than continuous ADT?

Recommendation: Two large randomized Intergroup studies are ongoing and intermittent androgen blockade should still be considered experimental.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

There were 10 randomized controlled trials, six systematic reviews, and one Markov model available to inform the guidelines.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

#### Bilateral Orchiectomy

Palliation begins quickly following orchiectomy. The procedure eliminates potential problems of patient compliance with medical therapies, and the relative cost of the procedure is low.

#### Luteinizing Hormone Releasing Hormone (LHRH) Agonists

Testosterone levels are usually within the castrate range 3 to 4 weeks after the first injection. Psychologically, these agents are easier for some men to tolerate than bilateral orchiectomy. Furthermore, while testosterone levels may not return to the same levels after prolonged use of luteinizing hormone releasing hormone (LHRH) agonists, the symptoms of hypotestosteronemia usually resolve 6 to 9 months after the cessation of therapy.

#### Diethylstilbestrol (DES)

Diethylstilbestrol (DES) has the advantages of ease of administration as a daily oral pill, and avoidance of the psychological negatives of a surgical procedure and relatively low cost.

### Nonsteroidal Antiandrogens (NSAA)

Nonsteroidal antiandrogens (NSAA) are oral medications with reversible side effects once therapy has ceased. NSAA had equivalent overall survival (OS) compared to orchiectomy.

### Combined Androgen Blockade (CAB)

Three meta-analyses indicated that combined androgen blockade (CAB) may modestly prolong life.

## POTENTIAL HARMS

### Bilateral Orchiectomy

The procedure carries with it a small risk of surgical complications, such as wound infection, hematoma, and pain. A greater concern to many men is the emotional impact of the procedure. When given the choice of surgery or medical castration, most patients select medical approaches first. In addition, due to the hypotestosteronemia, patients may suffer from vasoactive symptoms, weight gain, mood lability, gynecomastia, fatigue, lassitude, cognitive changes, and/or loss of libido. Long-term castrate levels of testosterone can also induce osteopenia and hypercholesterolemia.

### Luteinizing Hormone Releasing Hormone (LHRH) Agonists

Luteinizing hormone releasing hormone (LHRH) agonists effectively cause hypotestosteronemia and therefore carry with them the side effects of castration.

### Diethylstilbestrol (DES)

Diethylstilbestrol (DES) is associated with significant cardiovascular (CV) toxicities, including myocardial infarction, stroke, and pulmonary embolism, especially at moderate to high doses. The drug is no longer commercially available in North America.

### Nonsteroidal Antiandrogens (NSAA)

Overall, withdrawals due to adverse events occurred in 4 to 10% of patients. During single-agent therapy, significant gynecomastia and breast pain were reported (in up to 39% of patients). Hepatotoxicity has been reported with all NSAAs.

### Steroidal Antiandrogens

Liver toxicity has been recognized as a complication of long-term cyproterone acetate use.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

Luteinizing hormone releasing hormone (LHRH) agonists are contraindicated as monotherapy in men with impending spinal cord compression, urinary obstruction, or pain due to the potential for exacerbating symptoms.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

The American Society of Clinical Oncology (ASCO) considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient´s individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease for which better therapy is sorely needed. Insofar that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

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Jr, Bennett CL, Scher HI. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. J Clin Oncol 2004 Jul 15;22(14):2927-41. [59 references] PubMed

## ADAPTATION

Not applicable: The guideline was not adapted from another source.

## DATE RELEASED

2004 Jun 7

## GUIDELINE DEVELOPER(S)

American Society of Clinical Oncology - Medical Specialty Society

## SOURCE(S) OF FUNDING

American Society of Clinical Oncology (ASCO)

## GUIDELINE COMMITTEE

American Society of Clinical Oncology (ASCO) Metastatic Prostate Cancer Expert Panel

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Howard I. Scher, MD (Co-chair) Memorial Sloan-Kettering Cancer Center; Charles L. Bennett, MD, PhD (Co-chair) VA Chicago Health Care System-Lakeside & The Robert H. Lurie Comprehensive Cancer Center of Northwestern University; Edgar Ben-Josef, MD, University of Michigan; D. Andrew Loblaw, MD, MSc, Toronto Sunnybrook Regional Cancer Center; David S. Mendelson, MD, Arizona Cancer Center, Greater Phoenix Area; Richard Middleton, MD, University of Utah Medical School; Hank Porterfield US TOO, Inc; Stewart A. Sharp, MD, Danville Hematology & Oncology, Inc; Thomas J. Smith, MD, Massey Cancer Center, Virginia Commonwealth University; James Talcott, MD, MPH Massachusetts General Hospital; Mary Ellen Taplin, MD, University of Massachusetts Medical Center; Katherine S. Virgo, PhD, MBA, Saint Louis University & Department of Veterans Affairs Medical Center; Nicholas J. Vogelzang, MD, Nevada Cancer Institute; James L. Wade III, MD, Cancer Care Specialists of Central Illinois

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Owns stock (not including shares held through a public mutual fund): Howard I. Scher, Genta. Acted as a consultant within the last 2 years: Thomas J. Smith, Medtronic; Nicholas J. Vogelzang, Praecis, Abbott, Lilly, Advanced Life Sciences, EMD, Merck XGA, OSI, Pharmacia; Howard I. Scher, Sanofi-Synthelabo. Performed contract work within the last 2 years: Thomas J. Smith, Medtronic, Institute Medicini. Received more than $2,000 a year from a company for either of the last 2 years: Thomas J. Smith, Medtronic, Institute Medicini; Mary Ellen Taplin, AstraZeneca; Nicholas J. Vogelzang, Abbott, Praecis, Lilly, EMD; Howard I. Scher, AstraZeneca, Aventis.

## GUIDELINE STATUS

This is the current release of the guideline.

## GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Society of Clinical Oncology (ASCO) Web site.

Print copies: Available from ASCO, Health Services Research, 1900 Duke Street, Suite 200, Alexandria, VA 22314.

## AVAILABILITY OF COMPANION DOCUMENTS

None available

## PATIENT RESOURCES

The following is available:

- Hormone therapy for advanced prostate cancer. Alexandria (VA): American Society of Clinical Oncology; 2004. 14 p.

  Electronic copies: Available from the American Society of Clinical Oncology (ASCO) Web site.



## NGC STATUS

This NGC summary was completed by ECRI on August 11, 2004. The information was verified by the guideline developer on August 13, 2004.

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